

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No. : **09/328,975**
Applicants : **Jon A. Wolff et al.**
Filed : **06/09/1999**
Art Unit : **1635**
Examiner : **Schnizer, Richard A.**
Docket No. : **Mirus009**

For: Charge Reversal of Polyion Complexes

Commissioner of Patents
PO Box 1450
Alexandria, VA 22313-1450

APPELLANT'S BRIEF under 37 CFR 1.192

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i. Real party in interest:

The real parties in interest are: Jon A. Wolff, Vladimir S. Trubetskoy, Aaron G. Loomis, R Paul M. Slattum, Sean D. Monahan, James E. Hagstrom, Vladimir G. Budker and, by assignment, Mirus Corporation, which has changed its name to MirusBio Corporation, incorporated under the laws of the State of Delaware and located at 505 South Rosa Road, Madison, WI 53719.

ii. Related appeals and interferences:

There are no interferences known to appellant, the appellant's legal representative, or assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

iii. Status of Claims:

Claims 1, 3, 5, 7 have been rejected and are hereby appealed.

Claim 6 is objected to.

Claim 8 is allowed.

Claims 2, 4, and 9-19 have been canceled.

iv. Status of amendments:

An amendment was filed subsequent to the date of the final rejection. The amendment was entered and the amended claims were rejected.

v. Summary of claimed subject matter:

Cationic polymers are mixed with polynucleotides to form complexes of polynucleotide-polymer which interact by non-covalent, electrostatic charges. These complexes result in a net charge that is less negative than the polynucleotide prior to complexation. An anionic second polymer is then added to the mix to non-covalently attach to the cationic polymer/polynucleotide complex thus causing a net charge shift in the negative direction. The process is called "recharging" (another layer having a different charge) a polynucleotide. The resulting recharged complex can be formed with an appropriate amount of charged polymer such that the resulting complex has a net negative, positive or neutral charge (specification page 17, line 29 to page 18, line 7).

Nucleic acid at the core of tertiary complexes remains condensed, in the form of particles ~ 50 nm in diameter. Polynucleotides, cationic polymers and anionic polymers bind non-covalently in 1:1:1 complex to provide a net negative charge to the entire complex. Such small negatively charged particles are useful for gene transfer applications (specification page 18, lines 17-24).

The interaction between the charges located on the two polymer layers can be influenced with ions added to the system. With the appropriate ion, the layers can be made to disassociate from one another as the ion diffuses from the complex into the cell in which the concentration of the ion is low -- an ion gradient (specification page 19, lines 19-27).

vi. Grounds of rejection to be reviewed on appeal:

Whether claims 1, 3, 5, and 7 are unpatentable under 35 U.S.C. 103(a), for being unpatentable when considering Degols *et al.*, Leonetti *et al.* and Wiethoff *et al.*

Whether claims 1, 3, 5, and 7 are unpatentable under 35 U.S.C. 103(a) are unpatentable when considering Wu *et al.* and Degols *et al.*

vii. Argument:

(1) Rejection of the Claims under 35 U.S.C. 103(a):

(A) Rejection of claims 1, 3, 5, and 7 under §103 as being unpatentable over Degols *et al.* in view of Leonetti *et al.*, taken with the evidence of Wiethoff *et al.* on page 2 of the Action:

The §103 rejection is based upon the Degols *et al.* reference as the basic reference. However the Degols *et al.* reference teaches away from Applicants' specification and claims.

Applicants claim requires that a polycation be associated with a nucleic acid via a non-covalent interaction. Conversely, the Degols *et al.* reference requires that the polycation be covalently linked to the nucleic acid (see the ABSTRACT; p. 945, column 1, INTRODUCTION; p. 945, MATERIALS AND METHODS, Oligomers synthesis and covalent linkage to PLL, and throughout the paper).

In the Degols *et al.* reference on page 945, INTRODUCTION, they state that "in previous works, we have shown that antisense oligomers covalently linked PLL" inhibit VSV. The authors cite Lemaitre *et al.*, a previous publication by one of the authors, (1987) Proc. Natl. Acad. Sci. USA 84, 648-652 to provide authority. On page 948, DISCUSSION, the authors state they have "previously described that the conjugation to PLL potentializes the antiviral effects of an antisense oligomer directed against a VSV mRNA" again citing their previous publication as authority.

On page 650 of the citation, Lemaitre *et al.* states "In addition, no significant antiviral activity was observed when L929 cells were incubated with a mixture of poly(L-lysine) and 5' end sequence oligomers. In agreement with our previous data on (2'-5')(A)_n oligonucleotides (21), this result demonstrates that a covalent linkage of the oligodeoxyribonucleotide to poly(L-lysine) is necessary to obtain a biological activity."

The authors are clear in pointing out that a covalent linkage between the oligomers and polycations is necessary. This teaches away from Applicants' claims which specify a "non-covalent" interaction. Therefore, the Degols et al. reference supports Applicants' position rather than acting as § 103 prior art.

(2) Rejection of the Claims under 35 U.S.C. 103(a):

(A) Rejection of claims 1, 3, 5, and 7 under § on page 4 of the Action:

The § 103 rejection is based upon Wu *et al.* in view of Degols *et al.*

The § 103 rejection is based upon the Degols *et al.* reference as the basic reference. However the Degols et al. reference teaches away from Applicants' specification and claims.

Applicants claim requires that a polycation be associated with a nucleic acid via a non-covalent interaction. Conversely, the Degols et al. reference requires that the polycation be covalently linked to the nucleic acid (see the ABSTRACT; p. 945, column 1, INTRODUCTION; p. 945, MATERIALS AND METHODS, Oligomers synthesis and covalent linkage to PLL, and throughout the paper).

In the Degols et al. reference on page 945, INTRODUCTION, they state that "in previous works, we have shown that antisense oligomers covalently linked PLL" inhibit VSV. The authors cite Lemaitre et al., a previous publication by one of the authors, (1987) Proc. Natl. Acad. Sci. USA 84, 648-652 to provide authority. On page 948, DISCUSSION, the authors state they have "previously described that the conjugation to PLL potentializes the antiviral effects of an antisense oligomer directed against a VSV mRNA" again citing their previous publication as authority.

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linkage of the oligodeoxyribonucleotide to poly(L-lysine) is necessary to obtain a biological activity."

The authors are clear in pointing out that a covalent linkage between the oligomers and polycations is necessary. This teaches away from Applicants' claims which specify a "non-covalent" interaction. Therefore, the Degols et al. reference supports Applicants' position rather than acting as § 103 prior art.

viii. Claims Appendix:

1. A process for delivering a nucleic acid to a cell *in vivo*, comprising:
 - a) forming a composition consisting of a nucleic acid associated via a non-covalent ionic interaction with a polycation in a solution wherein the composition has a net charge less negative than the nucleic acid;
 - b) ionically associating a polyanion with the composition of step a) in sufficient amount to form a complex having a net negative charge;
 - c) inserting the complex into a mammal;
 - d) delivering the complex to the cell.
2. (canceled)
3. The process of claim 1 wherein the polycation is selected from the group consisting of polylysine and polyethylenimine.
4. (canceled)
5. The process of claim 1 wherein the polyanion comprises a molecule selected from the group consisting of succinylated PLL, succinylated PEI, polyglutamic acid, polyaspartic acid, polyacrylic acid, polymethacrylic acid, dextran sulfate, heparin, hyaluronic acid, DNA, RNA, and negatively charged proteins.
6. The process of claim 1 wherein the polyanion comprises a block co-polymer.
7. The process of claim 1 wherein the polyanion comprises a molecule selected from the group consisting of pegylated derivatives, pegylated derivatives carrying specific ligands, block copolymers, graft copolymers and hydrophilic polymers.

8. A tertiary complex for delivering a nucleic acid to a cell *in vivo*, comprising:
- a) the nucleic acid;
 - b) a polycation polymer complexed with the nucleic acid; and,
 - c) a polyanion polymer, having more than 80 monomer units, complexed with the polycation via ionic interaction, wherein the polyanion polymer is not the nucleic acid of a) and the polyanion and the polycation polymers comprise block co-polymers.

9-19. (canceled)

ix. Evidence appendix:

None

x. Related proceedings appendix:

None

Pages 1-14 are
respectfully submitted,

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I hereby certify that this correspondence is being transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as express mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this date: February 22, 2007.

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